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ABSTRACT

The flow between compartments in physical and biological systems is treated as a special case of a more general theory of transitions between any two distinct sets $A, \bar{A}$. Interest is focused on the <u>flow rate</u> from each set, i.e., the rate at which elements from that set appear in the other; and on the entry rate from each, i.e., the rate at which elements from the set leave to enter the region not part of either set. In particular, the two flow rates are completely determined by means of explicit expressions for their rates (Theorem I) and difference (Theorem II) in terms of the two entry rates. An application to biological transport problems extends a result of Dantzig and Pace [2] by demonstrating that for a system of channels each narrow enough to effect a "lining-up" of particles, <u>counter-gradient flows</u> may result, i.e., flows for which the flow rate is greatest from the compartment with the smallest entry rate.

ON STEADY-STATE INTERCOMPARTMENTAL FLOWS

In this paper, we study the flow between compartments in physical and biological systems as a special case of a more general theory of transitions between any two distinct sets A, $\bar{A}$. We define a mesh between A, $\bar{A}$ to be any sequence of disjoint sets

$$A = S_0, S_1, \ldots, S_n, S_{n+1} = \bar{A}$$

with the property that an element of any S_k may transition to other sets only by a sequence of forward and backward movements between consecutive sets. Elements of S_0 may <u>enter</u> the <u>interior</u> of the mesh by transitioning to S_1, and the rate at which this occurs is denoted E and called the <u>forward entry rate</u>. Similarly, elements of S_{n+1} may enter the interior of the mesh by transitioning to S_n, and this <u>backward entry rate</u> is denoted $\bar{E}$. Elements which enter the interior from S_0 are called <u>a-elements</u> until they <u>leave</u> the interior of the mesh either by dropping back from S_1 to S_0, which occurs with rate R, called the <u>return</u> rate, or by transitioning from S_n to S_{n+1}, which occurs with rate F, called the <u>forward flow</u> rate. Between entering the interior of the mesh and leaving it, either by dropping back into A or flowing into $\bar{A}$, an element may transition by a sequence of <u>forward</u> steps, from S_k to S_{k+1}, and <u>backward</u> steps, from S_k to S_{k-1}. Similarly, <u>$\bar{a}$-elements</u> may enter the interior of the mesh from S_{n+1} and leave either by dropping back from S_n to S_{n+1}, with rate $\bar{R}$, or by transitioning from S_1 to S_0, with rate $\bar{F}$.

A set is said to have <u>steady content</u> if its content of a-elements and of

$\bar{a}$-elements is independent of time.

A mesh is said to have <u>steady content</u> if

(1) $$E = F + R \ , \ \bar{E} = \bar{F} + \bar{R}$$

always; i.e., if the union of the sets $S_1,\ldots,S_n$ has steady content.

A mesh is called <u>Markovian</u> if for any $k=1,\ldots,n$, the probability of <u>direction</u> of movement of an element of S_k, from S_k to an adjacent set, depends only on the direction from which it entered, and not on any other aspect of its past history. For such meshes, for elements which entered S_k on a forward step, let α_k be the probability that the direction of its next movement will continue to be forward, and let $(1-\alpha_k)$ be the probability that it will be backward. For elements which entered S_k on a backward step, let β_k be the probability that the direction of its next movement will continue to be backward, and let $(1-\beta_k)$ be the probability that it will be forward.

A Markovian mesh is said to be in <u>steady-state</u> if all α_k , β_k are independent of time; and if for every $k = 1,\ldots,n$, the set S_k has steady content.

We can now prove:

THEOREM 1: <u>For Markovian meshes in steady-state, the ratio of flow rates between compartments A and $\bar{A}$ is given by the equation</u>

$$\frac{\bar{F}}{F} = \frac{\bar{E}}{E} \cdot \frac{\alpha_1\ldots\alpha_n}{\beta_1\ldots\beta_n} \quad .$$

For example, if A and $\bar{A}$ represent physical compartments connected by a channel such that the movement of elements through the channel is unaffected by the presence of other elements in the channel, then for any mesh that might be defined by subdividing the channel it follows that $\alpha_k = \beta_k = 1$ for all k; and hence the flow rates are proportional to the entry rates. This corresponds to Fick's law for free diffusion. On the other hand, as in [2] and [3], the channel might instead be so narrow that elements line up in a single file of n elements, and in this case the direction of next movement of any element in the channel will be the same as the next entry into the channel as a whole. Thus the ratios $\frac{\alpha_k}{1-\alpha_k} = \frac{E}{\bar{E}}$ and $\frac{1-\beta_k}{\beta_k} = \frac{E}{\bar{E}}$, whence $\frac{\alpha_k}{\beta_k} = \frac{E}{\bar{E}}$. Hence in the case of narrow channels, it follows from the theorem that $\frac{F}{\bar{F}} = \left(\frac{E}{\bar{E}}\right)^n$, so that the larger n is, the more unidirectional the flow becomes, always favoring the direction of the larger entry rate.

The proof of the theorem is by induction, and is clear for $n = 1$. We assume the theorem true for $n = k-1$, and apply it to the mesh $S_0', S_1', \ldots, S_k'$, defined by

$$S_0' = A,\ S_1' = S_1, \ldots, S_{k-2}' = S_{k-2},\ S_{k-1}' = S_{k-1} \cup S_k,\ S_k' = \bar{A},$$

where $S_{k-1} \cup S_k$ denotes the union of the two sets S_{k-1} and S_k. This mesh is also Markovian and in steady-state. We obtain by the inductive assumption that

$$\frac{F}{\bar{F}} = \frac{E}{\bar{E}} \cdot \frac{\alpha_1 \cdots \alpha_{k-2}\alpha_{k-1}'}{\beta_1 \cdots \beta_{k-2}\beta_{k-1}'} , \tag{2}$$

where α_{k-1}' is the probability that an element which transitions from

S_{k-2} to S_{k-1} will, if it leaves $S'_{k-1} = S_{k-1} \cup S_k$, next transition to S_{k+1}; and β'_{k-1} is the probability that an object which transitions from S_{k+1} to S_k will, if it leaves $S_{k-1} \cup S_k$, next transition to S_{k-2}. It is easily verified that α'_{k-1} is given by the infinite sum

$$\alpha_{k-1}\alpha_k + \alpha_{k-1}(1-\alpha_k)(1-\beta_{k-1})\alpha_k + \ldots + \alpha_{k-1}(1-\alpha_k)^p(1-\beta_{k-1})^p\alpha_k + \ldots,$$

whence

$$\alpha'_{k-1} = \frac{\alpha_{k-1}\alpha_k}{1-(1-\alpha_k)(1-\beta_{k-1})} \quad . \tag{3}$$

Similarly, we obtain that

$$\beta'_{k-1} = \frac{\beta_{k-1}\ \beta_k}{1-(1-\alpha_k)(1-\beta_{k-1})} \quad ; \tag{4}$$

and the theorem is immediate upon substitution of (3), (4) into (2).

In physical steady content situations, we are often interested in meshes that have the <u>transfer</u> property; i.e., that the rate E at which a-elements enter S_1 from S_0 is equal to the total rate $F+\bar{R}$ at which a- and $\bar{a}$-elements leave S_n to go into S_{n+1}; and the rate $\bar{E}$ at which $\bar{a}$-elements enter S_n from S_{n+1} is equal to the total rate $\bar{F}+R$ at which a- and $\bar{a}$-elements leave S_1 to go into S_0. The analytical definition of this property,

$$E = F + \bar{R} \quad , \quad \bar{E} = \bar{F} + R \quad ,$$

taken with (1), provides an immediate characterization of these meshes:

THEOREM II: <u>Any mesh with steady content has the transfer property if and only if</u>

$$F - \bar{F} = E - \bar{E} \tag{5}$$

<u>is satisfied</u>.

Since any mesh in steady-state has steady content, we obtain trivially for this important case the

COROLLARY: <u>In steady-state, a mesh satisfies the transfer property if and only if the difference in flow rates between A and $\bar{A}$ is equal to the difference in entry rates</u>.

Applications:

Some investigators, in modeling transport in biological systems, in particular [2] the active transport of sodium and potassium ions and [3] the exchange of potassium and its labelled isotope across the membranes of living cells, have postulated as part of their models systems of channels, each channel narrow enough to effect a "lining up" of particles. Such channels, when the system is physically in steady-state, are either at rest, in which case they contain a fixed number of particles ordered in some way; or, they are in a transient state caused by the entry of a particle into one end or the other of the channel from one of the two compartments $A, \bar{A}$ between which transport is taking place. When an entry does occur, it sets off a chain reaction which is idealized as just one particle moving at any time. As it approaches the particle which at rest was in the $k^{\underline{th}}$ position, it either, with probability t_k, passes it and proceeds on to the next particle; or it <u>strikes</u> and replaces the $k^{\underline{th}}$ particle, which itself then moves on to the next. The transfer property thus holds for such channels, so that the difference of their flow rates is equal to the difference of their entry rates (Corollary to Theorem II).

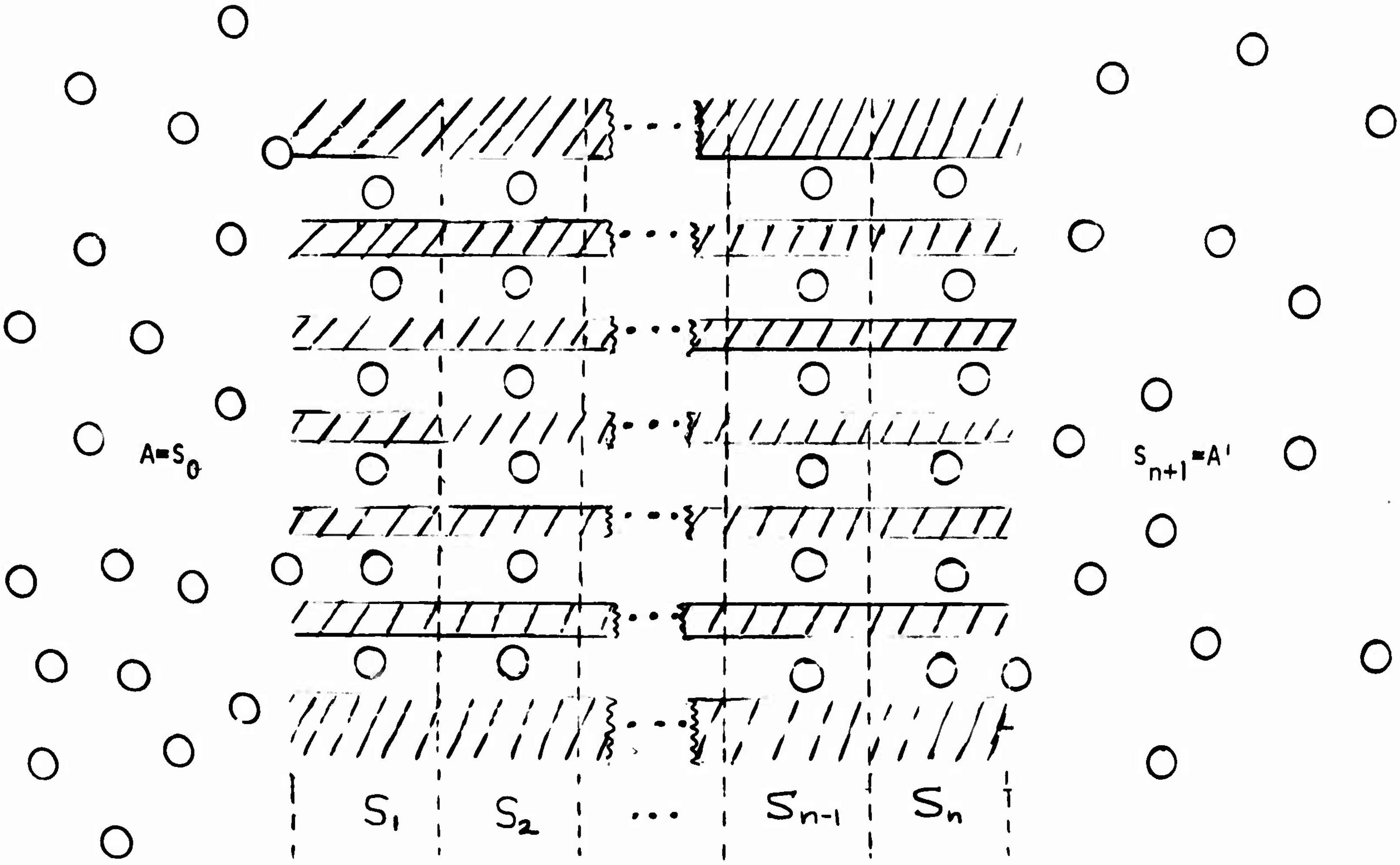

Fig. 1.

Let us now consider the ratio of the flow rates. We define a mesh [See Fig. 1.] between $A,\bar{A}$ by conceptually dividing each channel into n consecutive sections such that each section contains exactly one particle at rest. For simplicity, n is assumed the same for each channel, and the channels are assumed mutually exclusive. The set S_1 is defined as the union of first sections of the channels, i.e., those adjacent to S_0; the set S_2 is defined as the union of second sections, i.e. those adjacent to the first sections; and so forth. The mesh is Markovian; and in fact it is easy to see that

$$\alpha_k = t_k + (1-t_k)\frac{E}{E+\bar{E}}\ ,\ \beta_k = t_k + (1-t_k)\frac{\bar{E}}{E+\bar{E}}$$

because a particle striking and replacing the k^{th} particle has probability $\frac{E}{E+\bar{E}}$, when it is next struck, of moving towards the $(k+1)^{st}$ particle; and probability $\frac{\bar{E}}{E+\bar{E}}$ of moving towards the $(k-1)^{st}$ particle. Hence we obtain from Theorem 1 that

$$(6) \qquad \frac{F}{\bar{F}} = \frac{E}{\bar{E}} \cdot \prod_{k=1}^{n} \cdot \frac{E + t_k\bar{E}}{\bar{E} + t_k E} \ .$$

For channels so narrow that the particles line up in single file and it is not possible for one particle to pass another, it follows that $t_k = 0$ for all k. In this case, (6) was essentially given by Hodgkin and Keynes [3] and (5) by Dantzig and Pace [2], using methods quite different from ours. Bigelow [1] has obtained a generalization of their methods and results when t_k is the same non-zero constant for all k. The case $t_k=1$ corresponds to free diffusion, as noted earlier. The principal motive for such an approach in [2] and [1] is to demonstrate that flows against electrochemical gradients are possible within the rather simple framework of these models, and it suffices for the purpose of this paper to now qualitatively demonstrate this point in the most general case.

Counter Gradient Flows

When dealing with chemical solutions, it is necessary to consider from the same compartment entries of particles of different types, in particular different

chemical species. For each species i we then have "entr E_i from A and $\bar{E}_i$ from $\bar{A}$, with the total entry rates being given by

$$E = \sum_i E_i , \bar{E} = \sum_i \bar{E}_i \quad .$$

Further, we may also define "flow rates" F_i, $\bar{F}_i$ for each species, such that

$$F = \sum_i F_i \ , \ \bar{F} = \sum_i \bar{F}_i \ .$$

If we assume that within the mesh the behavior of an element is independent of its species, then the flow of a particular species F_s is in the same ratio to total flow as E_s is to total entries. Thus

$$\frac{F_s}{\Sigma F_i} = \frac{E_s}{\Sigma E_i} \ , \quad \frac{\bar{F}_s}{\Sigma \bar{F}_i} = \frac{\bar{E}_s}{\bar{E}} \ ;$$

and this, taken with (6), yields at once the ratio of flow rates

$$(7) \qquad \frac{F_s}{\bar{F}_s} = \frac{E_s}{\bar{E}_s} \prod_{k=1}^{n} \frac{E + t_k \bar{E}}{\bar{E} + t_k E} \quad .$$

As noted, in this development t_k, the probability of passing the particle in k^{th} position, is assumed independent of species. A more general model is under development where t_k depends on species.

We say a <u>counter-gradient flow</u> exists for a species i if the sign of $(F_i - \bar{F}_i)$ is opposite to that of $(E_i - \bar{E}_i)$. In other words, if $E_i > \bar{E}_i$, a counter-gradient flow will be said to exist if $F_i < \bar{F}_i$; and analogously for the case $E_i < \bar{E}_i$.

Let us consider a particular species $i=s$ for which $E_s > \bar{E}_s$ and investigate

the conditions for a counter-gradient flow to exist for this species. We first note that if the total flow $E > \bar{E}$, then

$$E + t_k\bar{E} \geq \bar{E} + t_k E$$

follows for $0 \leq t_k \leq 1$; and thus it follows from (7) that $\frac{F_s}{\bar{F}_s} > 1$, so that there is no counter-gradient flow for the species s. To paraphrase, we have shown that for the case $E_s > \bar{E}_s$, a counter-gradient flow can possibly exist only when the total entries by all species $\bar{E} > E$.

We thus address ourselves to the question, how must we adjust the ratio of total entry rates $r = \frac{E}{\bar{E}}$ to induce a counter-gradient flow for the species s, where $E_s > \bar{E}_s$? By definition, a counter-gradient flow exists for s if and only if $\frac{F_s}{\bar{F}_s} < 1$; or noting (7) if and only if

$$1 > \frac{\bar{E}_s}{E_s} > \lambda_1 \ldots \lambda_n, \tag{8}$$

where we have set

$$\lambda_k = \frac{E + t_k\bar{E}}{\bar{E} + t_k E} = \frac{r + t_k}{1 + rt_k} .$$

We assume that the probability t_k, $0 \leq t_k \leq 1$, of bypassing a particle in the passage is independent of the flow rates $E, \bar{E}$. It is easy to verify that λ_k is continuous and monotonically non-decreasing in $r = \frac{E}{\bar{E}}$, and ranges between its extreme values 1 and t_k as r ranges between 1 and 0. Thus it follows at once that the product $\lambda_1 \ldots \lambda_n$ is continuous and monotonically non-decreasing in mr; and ranges between its extremes 1 and $t_1 \ldots t_n$ as r ranges between 1 and 0, whence

THEOREM III: <u>A necessary and sufficient condition that the ratio</u> $r = \frac{E}{\bar{E}}$ <u>can be adjusted so that a counter-gradient flow exists for the species</u> s, <u>where</u> $\frac{\bar{E}_s}{E_s} < 1$, <u>is that</u>

$$1 > \frac{\bar{E}_s}{E_s} > t_1 \dots t_n. \tag{9}$$

(Note that the case $\frac{\bar{E}_s}{E_s} > 1$ is easily handled with this theorem by an elementary notational exchange of barred and unbarred quantities). The necessity of the condition follows from (8) and the relation just obtained, that is $\lambda_1 \dots \lambda_n \geq t_1 \dots t_n$. To show sufficiency, suppose (9) holds. Because $\lambda_1 \dots \lambda_n$ ranges continuously from 1 to $t_1 \dots t_k$, there always exist by the intermediate value theorem, $\lambda_1, \dots, \lambda_n$ such that (8) holds.

For the extreme case of narrow channels, for example, $t_k = 0$ for all k, so that (9) always holds. In that case, it is easy to see that counter-gradient flows will exist if $r = \frac{E}{\bar{E}}$ is chosen so that $r^n < \frac{\bar{E}_s}{E_s}$. At the other extreme, for "open" channels (i.e. free diffusion) where all $t_k = 1$, condition (8) never holds and hence counter-gradient flows can never occur.

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